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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/043,658
Filing Date: January 09, 2002
Appellant(s): OLSON, ERIC N.

UNIVERSITY OF TEXAS, AUTSIN TEXAS AND MYOGEN INC. (NOW GILEAD SCIENCES)
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 1/12/07 appealing from the Office action mailed 5/12/06.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

Xu et al. MEF2A and MEF2C induce dilated cardiomyopathy in transgenic mice, JBC 2006, pp. 1-18. Manuscript M510217200

Mora et al. The MEF2A isoform is required for striated muscle-specific expression of the insulin -responsive GLUT4 glucose transporter The Journal of Biological Chemistry, vol275, no.21 (2000), pp. 16323-16328

Black et al. Cooperative transcriptional activation by the neurogenic basic helix-loop-helix protein MASH1 and members of the myocyte enhancer factor-2 (MEF2) family The Journal of Biological Chemistry, vol271, no. 43 (1996), pp. 26659-26663

Zhang et al. Class II histone deacetylases act as signal-responsive repressors of cardiac hypertrophy Cell, vol.110 (August 23, 2002), pp. 479-488

McKinsey et al. Signaling chromatin to make muscle Curr. Opin. Cell Biol. vol14, no. 6 (December 2002) abstract

Kobarg et al. MEF2C DNA-binding activity is inhibited through its interaction with the regulatory protein Ki-1/57 FEBS Lett. vol579, no. 12 (May 2005) pp. 2615-22.

Olson Undermining the endothelium by ablation of MAPK-MEK signaling JCI (April 2004) vol113, no. 8, pp.1110-1112.

Prassier et al. CaM kinase signaling induces cardiac hypertrophy and activates the MEF2 transcription factor in vivo JCI vol105, no. 10, (May 2000) pp. 1395-1406.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 4 and 9 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a prima facie case are discussed below.

The elected invention encompasses a method of treating hypertrophy in a cardiomyoctye comprising the steps of first decreasing the expression of MEF2 gene and further decreasing the expression of a gene that is upregulated by MEF2. The specification teaches that MEF2C is

important in vascular development during embryology, and absence of MEF2C in transgenic mice results in embryo death at E9.5 days. Further, an analysis of genes important in vascular development which contain promoters with MEF2 binding sites indicate that MEF2C alone is not important in the regulation of these genes because even in the absence of MEF2C these genes are expressed. Using promoter reporter constructs containing the MEF2 binding site, a correlation between hypertrophy and up-regulation of MEF2 binding/promoter activity is made by applicant (example 4). While evidence in the art at the time of filing teaches that cardiac hypertrophy has been shown to be controlled by a signaling pathway involving calcineurin and the transcription factor NFAT3, alternative pathways could also be involved (page 82). Based on the change of expression of the MEF2 reporter construct and its role in embryological vascular development it is proposed that HDAC and CaM Kinase signaling also may play a role in these processes. However, the art of record teaches that hypertrophy is a complex process of signal transduction and while MEF2 is activated during hypertrophy, there is no direct link between MEF2 causing the hypertrophy. Importantly, in view of the teaching of the specification and the art of record there are several issues regarding the ability to target MEF2 in treating hypertrophy. First, since multiple pathways exist that end in a hypertrophic state lacking any clear and distinct role for MEF2 in all these pathways (Olson JCI 113:1110-1112, 2004) it would appear that simply inhibiting MEF2 will have no affect. While MEF2 animal models have been important in defining the potential role of MEF2, they have served best to demonstrate that separate and distinct pathways exist that cause hypertrophy (Prassier et al. JCI 105(10):1395-1406, 2000). Additionally, it should be noted that MEF represents a family of encoded proteins of which only MEF2C has been implicated in endothelium cell survival, while study of the others have

further genes to target for inhibition. 35 U.S.C. § 112 requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art. In re Fisher, 166 USPQ 18, 24 (CCPA 1970). It is also well established in case law that the specification must teach those of skill in the art how to make and how to use the invention as broadly claimed. In re Goodman, 29 USPQ2d at 2013 (Fed. Cir. 1994), citing In re Vaeck, 20 USPQ2d at 1445 (Fed. Cir. 1991). Further, it is noted that the unpredictability of a particular art area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See Ex parte Singh, 17 USPQ2d 1714 (BPAI 1991). In the instant case, there is evidence that MEF2C plays a role in the signal transduction pathway that is activated during conditions that cause hypertrophy, however there is no nexus between this observation and the direct role of all the family members of MEF2 causing hypertrophy. While the evidence of record supports a role for MEF2 in signal transduction during hypertrophy the specification provides insufficient teaching and guidance that the therapeutic methods of treatment proposed would work.

The instant invention, as claimed, falls under the "germ of an idea" concept defined by the CAFC. The court has stated that, "patent protection is granted in return for an enabling disclosure, not for vague intimations of general ideas that may or may not be workable". The court continues to say that "tossing out the mere germ of an idea does not constitute an enabling disclosure" and that "the specification, not knowledge in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement". (See Genentech inc v. Novo Nordisk A/S 42 USPQ2d 1001, at 1005). The claimed methods of treatment constitute such a "germ of an idea" because a direct role of all the MEF2 family members causing hypertrophy has

provided no correlation. Second, while the evidence of record does indicate that MEF2 expression/activity goes up in response to signaling cascades associated with hypertrophy, from the evidence of record it is unclear whether decreasing MEF2 once a cell is hypertrophic will result in any affect. For example, even if overexpression of MEF2 was demonstrated to cause the hypertrophic state there is no evidence of record that reducing or removing the activity bfMEF2 will result in treatment by ameliorating the affect on the cell. However as discussed above, it should be noted that even as of 2004 the inventor acknowledges that it is still to be determined whether MEF2 is involved in the pathogenic mechanisms associated with endothelial disorders (third column, page 1111, Olson JCI 113:1110-1112, 2004). This is complicated even further by the fact that MEF2 alone does not regulate gene expression and as acknowledged by the instant specification these specific partners remain to be defined (page 5, top of page). Finally, the instantly claimed method requires further inhibiting genes upregulated by MEF2 however the instant specification does not identify any of these potential target genes (page 1404, top of first column, Prassier et al. JCI 105(10): 1395-1406, 2000). While the Examiner would acknowledge that the art of record teaches that family of MEF2 transcriptional factors regulate the expression of numerous muscle specific and growth factor inducible genes (for example Black et al. Ann Rev Cell Dev Bol 14:167-196), neither the art of record nor the instant specification teach which of these one should even begin to target to affect hypertrophy.
The instantly claimed method is based in part on the up-regulation of the MEF2 during hypertrophy and the important role of MEF2C in heart growth and development. However, the instant disclosure fails to provide a clear correlation that decreasing any MEF2 family member will affect hypertrophy. Further, the disclosure fails to provide any specific guidance to what

not been established. Further, there is no specific guidance to what further upregulated MEF2 genes should be subject to inhibition and that would result in treatment.

In view of the lack of guidance, working examples, breadth of the claims, the level of skill in the art and state of the art at the time of the claimed invention was made, it would have required undue experimentation to make and/or use the invention as claimed.

(10) Response to Argument

In response to appellants argument that in view of Xu et al. 2006 (Exhibit 1) (effective filing date of instant application is 11/12/98, filing date of the provisional application, 8 years before the article was published) that MEF2A and MEF2C have similar function, the argument is not found persuasive because while forms of MEF2 may have similar functions in other systems, there is no evidence in the specification as filed that anything besides MEF2C participates in the signaling pathway during hypertrophy. Moreover, the detailed analysis provided in the specification provides further evidence of the complexity and reliance of factors other than MEF2C in the signaling pathway during hypertrophy. Given this evidence one of skill in the art would not expect that trying to affect other isoforms would treat or be of any benefit in the claimed method. More specifically, in light of the phenotypes of transgenic animals overexpressing MEF developing hypertrophy, one conclude from the total teachings in Xu et al. that MEF2 is at best a primary response which results in a cascade of changes leading to hypertrophy. Once the cascade and consequent affect is present in a subject, there is no link nor post-filing evidence that affecting MEF2 would stop the consequences of the cascade, i.e. treat hypertrophy. Moreover, Xu et al. provide in vitro data demonstrating that MEF alone is not

sufficient to induce hypertrophy in vitro, and the role and requirement other factors (bridging pages 6-7) clearly indicating the complexity of the process. Furthermore, the teachings of Xu et al in total must be considered, not general lines out of context, as one of skill in the art would. In this case, the skilled artisan would view would not consider MEF to be a target, and clearly in vitro it appears to play no role in hypertrophy (noting that that broadly claim 1 encompasses an in vitro embodiment of affecting a cardiomyocyte cell). An analogy can be made to the biology in cancer where an aberrant gene or gene expression results in cancer formation, for example v-myc or ras expression models, however targeting these early factors that may trigger a cause are not effective targets once the transformation process to cancer has been established. As here, the evidence of record clearly indicates that overexpression of MEF can lead to hypertrophy in transgenic models, not in vitro as evidenced by Xu et al, however a myriad of factors are present and required for the end effect in a subject, where MEF is at best an initial signaling event not a protein that by itself causes the hypertrophy. Furthermore, there is nothing in the specification that would lead one of skill in the art to the teaching of Xu's articles published 8 years after the effective filing date of the instant specification

In response to appellant's argument that Mora (Exhibit 2) teaches that MEF2A and MEF2D form a heterodimer, suggesting a common role for these two proteins, the argument is not found persuasive because there is nothing in the specification teaching that MEF2A and MEF2D form a heterodimer. Mora does not disclose that the heterodimer is associated with hypertrophy. Mora teaches the association being involved in an insulin disorder. Furthermore, Mora teaches that "without any detectable MEF2A-MEF2A homodimers or MEF2A-MEF2C and MEF2C-MEF2D heterodimers (abstract)". Thus, the skilled artisan would not be able to

reasonably extrapolate from the teaching in the specification to MEF2A and MEF2D forming a heterodimer involved in hypertrophy.

In response to appellant's argument that Black (Exhibit 3) teaches that MEF2A, MEF2C, and MEF2D have similar functions with respect to interactions with MASH1 and E12, the argument is not found persuasive while the Examiner acknowledges that the art of record teaches that family of MEF2 transcriptional factors regulate the expression of numerous muscle specific and growth factor inducible genes. Neither the art of record nor the instant specification teach which of these should even begin to target to affect hypertrophy. The instantly claimed method is based in part on the up-regulation of the MEF2 during hypertrophy and the important role of MEF2C in heart growth and development, however, the instant disclosure fails to provide a clear correlation that decreasing any MEF2 family member will affect hypertrophy and fails to provide any specific guidance to what further genes to target for inhibition. Black teaches that, "MASH1 and MEF2A were able to activate transcription through either factor's binding site when only one factor was bound to DNA" (page 26663). However, another research group has shown that both MASH1 and MEF2A need to bound to DNA for activation through transcription (page 26663). The specification and prior art do not clarify why there are two results for activation of DNA using MASH1 and MEF2A and what mechanism is required in vivo for inhibiting hypertrophy.

In response to appellant's argument that two declarations (Exhibits 4-5) provide support for the enablement, the second declaration provided experiments with one month-old MEF2D knockout mice, the argument is not found persuasive there is no support in the specification for making and using MEF2D knockout mice. The specification contemplates four MEF2 genes in

ES cells and transgenic mice are inactivated and discuss the prior art teaching mice lacking MEF2C (pages 73-74). But, the specification does not discuss results with MEF2D knockout mice that would allow the skilled artisan to reasonable extrapolate from the generic contemplation in the specification to the teaching in the post-filing art (instant application claims priority to provisional application filed on 11/12/98). In addition, the Declaration filed on 5/11/05 states, "It is true that it has not been conclusively shown that direct inhibition of MEF2 ablates hypertrophy...(page 4, item 5)". Thus, the skilled artisan would not be able to reasonably extrapolate from the teaching in the specification to a MEF2D knockout mice being associated with hypertrophy.

In response to appellant's argument that the Declaration by McKinsey filed on 5/11/05 comes to an opposite conclusion of the examiner with regard to the teaching of enablement in view of Zhang (Exhibit 6) and McKinsey (Exhibit 7), the argument is not found persuasive because the conclusions of Zhang et al. (2002) clearly indicate the complexity of hypertrophy in the heart, and more specifically in the pathways that regulate the stress response (page 487, first column). Even with their experimental evidence Zhang et al. conclude that HDACs, not MEF2, "represent potential therapeutic targets" (page 487, first column). Similarly, McKinsey et al. provide evidence and conclude an importance of chromatin modifying enzymes in general, such as HDACs, for affecting muscle. The elected invention encompasses a method of treating hypertrophy in a cardiomyoctye comprising the steps of first decreasing the expression of MEF2 gene and further decreasing the expression of a gene that is upregulated by MEF2. From the evidence of record, since multiple pathways exist that end in a hypertrophic state lacking any

clear and distinct role for MEF2 in all these pathways (Olson JCI 113:1110-1112, 2004) one would conclude that simply inhibiting MEF2 will have no affect.

In response to appellant's argument that just because there are limitations with respect to gene therapy does not mean that one skill in the art cannot make and use the invention, the argument is not found persuasive because there are no working examples of the claimed method. At the time of filing, the specification was not considered enabled for the elected invention, method of decreasing the expression of MEF2 gene and further decreasing the expression of a genus of genes that is upregulated by MEF2 (elected on 4/5/04). See MPEP 2164.05(a), which recites the specification must be enabling as of the filing date (which would be 11/12/98). Secondly, with respect to methods required to practice the claimed invention, Examiner has acknowledged that working examples are not required, and would agree that specific guidance would not be required for methodology that is routine in the art. However, in this case, the methods relied upon for practicing the claimed invention as broadly claimed are not even clearly set forth in the claim nor the specification. Very importantly, no specific compounds are provided in the specification, nor is there any guidance to an end target except to the simplistic requirement that MEF2 function, any function, be affected, wherein this presumably results in treatment. The means and goal to this end are completely prophetic as evidenced by Example 5 of the specification (see page 77 of the specification). It is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of an invention in order to constitute adequate enablement, e.g. Genentech Inc. v. Novo Nordisk A/S, 108 F.3d 1361, 1366, 42, USPQ2d 1001, 1005 (Fed. Cir. 1997) and Enzo 188 F.3d at 1374, 52 USPQ2d at 1138. This is not a general secondary portion of the rejection because to practice the method as broadly

claimed, the specific materials needed to predictably practice the method as broadly claimed should be provided to provide at least a starting point for the skilled artisan. In this case, there is no indication that practicing the claimed method would use materials and/or methods known in the prior art, and to the contrary there is no art on the novelty indicating that such methods are known. Claim 9 recites using an anti-sense construct, however this is not a routine art accepted method, additionally noting that there is no guidance to what this construct would physically or functionally be, or how to effectively deliver a construct at therapeutic levels-or what a therapeutic level would even be as a target of reasonable experimentation. This is not a generalized dispersion or a requirement of efficacy of gene therapy as argued by Appellant, rather it is a necessity of satisfying the requirements of 35 USC 112, first paragraph, for the claimed method. The argument of the office is not a general one; rather it builds on the problems specifically associated with the hypothesis on which the claimed invention is based. It is again noted that besides the general proposal to use an anti-sense construct, and even then there is no specific teaching of the materials or the methods in the specification for one of skill in the art. It is noted that the courts have stated that reasonable correlation must exist between scope of exclusive right to patent application and scope of enablement set forth in patent application.

In response to appellant's argument that the expert declaration (McKinsey Declaration; Exhibit 4) and Xu et al. 2006 (Exhibit 1) support the position that down-regulating MEF2 would indeed be therapeutic of cardiac hypertrophy, the argument is not found persuasive because neither McKinsey nor Xu address whether or not practicing the claimed method (using a genus of nucleic acids to inhibit decreasing the expression of MEF2 gene and further decreasing the expression of a gene that is upregulated by MEF2) would not require an undue amount of

experimentation. Neither the Declaration nor Exhibit 1 teach the skilled artisan to construct nucleic acids that target transcription or post-transcription to down regulate MEF2A to treat hypertrophy (See Mora, page 16328). In addition, the art of record does not indicate that it was routine for the skilled artisan to construct nucleic acids that target transcription or post-transcription to down regulate MEF2A to treat hypertrophy in cardiac cells.

In response to appellant's argument that the generic contemplation (pages 23-30) in the specification provides enablement for using a genus of materials in the claimed invention, the argument is not found persuasive because the generic contemplation (pages 23-30) does not teach the skilled artisan what nucleic acids can be used in the claimed method. For example, the skilled artisan would have to construct nucleic acids that target transcription or post-transcription and determine what nucleic acids down regulate MEF2A and treat hypertrophy (See Mora, page 16328). In view of the lack of a working example in the specification for the claimed method and that it was not routine in the art to practice the claimed method, the skilled artisan would have to perform an undue amount of experimentation to practice the elected and examined invention. It is noted that patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable (See Brenner v. Manson, 383 U.S. 519, 536, 148 USPQ 689, 696 (19663, Stating, in context of the utility requirement, that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion") Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention.

There is no reasonable detail provided in the specification for the skilled artisan to carry out the invention without an undue amount of experimentation.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

Brian Whiteman

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